PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study Protocol of a Randomized controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypofractionation (PRIME TRIAL)
AUTHORS	Murthy, Vedang; Mallick, Indranil; Gavarraju, Abhilash; Sinha, Shwetabh; Krishnatry, Rahul; Telkhade, Tejshri; Moses, Arunsingh; Kannan, Sadhna; Prakash, Gagan; Pal, Mahendra; Menon, Santosh; Popat, Palak; Rangarajan, Venkatesh; Agarwal, Archi; Kulkarni, Sheetal; Bakshi, Ganesh

VERSION 1 - REVIEW

REVIEWER	Glenn Bauman London Health Sciences Centre, Canada
REVIEW RETURNED	08-Oct-2019

GENERAL COMMENTS	The authors should clarify how these patients will be staged. In the "strengths" they say PMSA PET CT will be done on all patients but in the protocol the staging studies are not clearly outlined and in some areas indicates PET CT and/or MRI - these are not equivalent studies. As PSMA PET CT is significantly more sensitive for detecting nodal disease, if PSMA PET CT is not going to be done on all men, then men should be stratified by PSMA PET CT use prior to randomization. In the discussion a paragraph discussing FASTR and SATURN is repeated and should be edited out.

REVIEWER	Thomas ZILLI Geneva University Hospital
REVIEW RETURNED	04-Nov-2019

GENERAL COMMENTS	The authors report the study protocol of a prospective phase III trial exploring the role of extreme pelvic hypofractionation versus moderate hypofractionation. The study has been approved by the local ethical committee and it will randomize 434 patients with locally advanced or node positive prostate cancer. However, it is not clear if the study is already recruiting. Many issues should be discussed and commented before to accept the study protocol for publication:

	-Page 3. “Strenghts”: use of PSMA PET/CT for all patients. This point does not figure as inclusion criteria. Indeed, it is not clear how patients are staged. It seems that the pre-treatment evaluation can include all the imaging methods. Modern imaging can impact the detection of nodal disease compared to standard imaging techniques. This should be mentioned and commented and probably used as stratification criteria. -Page 7: the authors propose 68 Gy in 25 fractions of 2.72 Gy as standard. Please comment on this choice and report some literature justifying the 80% biochemical disease control at 4-years used for power calculations. -Inclusion criteria: please define how a suspicious node is defined (size, uptake?) -Inclusion criteria include the compliance to fulfill the QoL questionnaires. This QoL part is normally considered optional. Please comment on that. -Inclusion criteria: patients undergoing orchiectomy are allowed. Why to include long-life androgen deprivation for patients with locally advanced or node positive disease normally treated with 18-36 months ADT? How many patients are expected to be in this group? -Exclusion criteria: why allow to include in the study patients with a life expectancy between 3 and 5 years? Please comment on that -Page 5: please add the stratification criteria. -Page 7: treatment duration: please comment on OTT duration of 7 days with a treatment delivered every-other day (OTT expected minimum 9 days). Considering that OTT can impact tolerance of SBRT schedules (cfr King’s series or the PATRIOT trial), it seems risky to extend the study protocol at the use of different OTT schedules. -Page 8: are fiducials used for IGRT purposes? If invade, are the whole SV included in the high-dose volume. -Please describe when EORTC or CTCAE grading scales are used (EORTC for acute and CTCAE for late side effects?) -Pages 15 and 16: This section is a duplicate of the section already present on pages 13 and 14. -Table 2. Doses constraints seems quite difficult to be achieved especially if the SV are included and nodes are boosted. Could you provide some data justifying the use of these dose constraints? -Please comment on how the boost to the positive nodes is considered. This point is not clear and it can introduce large biases in the study. -Many references should be updated: ex ref 8 (published the last year on Lancet). Ref 7. Please add a reference for the PACE B study.

	-Please add a table with the inclusion and exclusion criteria including the timeline of the study.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

1. The authors should clarify how these patients will be staged. In the "strengths" they say PMSA PET CT will be done on all patients but in the protocol the staging studies are not clearly outlined and in some areas indicates PET CT and/or MRI - these are not equivalent studies. As PSMA PET CT is significantly more sensitive for detecting nodal disease, if PSMA PET CT is not going to be done on all men, then men should be stratified by PSMA PET CT use prior to randomization.

A. All eligible patients will undergo a PSMA PET CT at baseline for staging evaluation and it has been amended to be included in the inclusion criteria.

2. In the discussion a paragraph discussing FASTR and SATURN is repeated and should be edited out.

A. Repeat paragraph discussing FASTR and SATURN has been edited out.

Response to Reviewer 2

1. The authors report the study protocol of a prospective phase III trial exploring the role of extreme pelvic hypofractionation versus moderate hypofractionation. The study has been approved by the local ethical committee and it will randomize 434 patients with locally advanced or node positive prostate cancer. However, it is not clear if the study is already recruiting.

A. This is an ongoing, noninferiority, multicentre, randomized trial which is presently accruing patients.

2. Page 3. “Strengths”: use of PSMA PET/CT for all patients. This point does not figure as inclusion criteria. Indeed, it is not clear how patients are staged. It seems that the pre-treatment evaluation can include all the imaging methods. Modern imaging can impact the detection of nodal disease compared to standard imaging techniques. This should be mentioned and commented and probably used as stratification criteria.

A. All eligible patients will undergo a PSMA PET CT at baseline for staging evaluation and it has been amended to be included in the inclusion criteria.

3. Page 7: the authors propose 68 Gy in 25 fractions of 2.72 Gy as standard. Please comment on this choice and report some literature justifying the 80% biochemical disease control at 4-years used for power calculations.

A. The BED for this dose fractionation is in the range of 180-200Gy and the outcomes of this schedule has been published from our institute.

[Murthy V, Krishnatry R, Mallik S, Master Z, Mahantshetty U, Shrivastava S. Helical tomotherapy-based hypofractionated radiotherapy for prostate cancer: a report on the procedure, dosimetry and preliminary clinical outcome. Journal of cancer research and therapeutics. 2013 Apr 1;9(2):253.].

This schedule has also been used in the department for the last decade including as part of a RCT comparing Prostate Only or Pelvic RT in High Risk Prostate Cancer (POP RT) (https://clinicaltrials.gov/ct2/show/NCT02302105).

[Murthy V, Bhatia J, Kannan S, Gurav P, Krishnatry R, Chourasiya D, Prakash G, Bakshi G, Menon S, Mahantshetty U. PV-0629 Late toxicity and PROMs in pelvic or prostate RT in high risk prostate cancer: A randomized trial. Radiotherapy and Oncology. 2019 Apr 1;133: S335].

We chose this dose schedule based on our institutional standard in view of locally advanced (high risk and very high risk) nature of these patients. The EQD2 for said dose fractionation is approximately in the range of 78-82 Gy and the outcomes and safety of such schedules have been published from our institute.

The assumption of 80% BFFS in the standard arm was based on the results of similar studies of high risk node negative cancer like STAMPEDE [James ND, et al JAMA oncology. 2016 Mar showing a 5-year OS 90% and 5 year FFS 76% in N0 cohort and 5-year OS 82% and 5 year FFS of 65% in N+ cohort] and PRO 7 [Mason MD, et al, JCO 2015; 5-year OS of 84%. PRO7 had no mandatory nodal staging] and our own data (unpublished) which showed a 5-year BFFS of about 85%. As this study is recruiting high risk and node positive patients also, the upper limit of 80% was chosen.

4. Inclusion criteria: please define how a suspicious node is defined (size, uptake?)
A. A suspicious node on PSMA PET CT is defined as having a dimension of ≥ 1cm in the short axis and SUVmax ≥ 3.0 based on the morphological and metabolic assessment by a Nuclear medicine specialist in Uro Radiology.

5. Inclusion criteria include the compliance to fulfill the QOL questionnaires. This QOL part is normally considered optional. Please comment on that.
A. We appreciate this comment from the reviewer. The QOL is considered optional and not mandatory and it has been amended accordingly in the inclusion criteria.

6. Inclusion criteria: patients undergoing orchiectomy are allowed. Why to include long-life androgen deprivation for patients with locally advanced or node positive disease normally treated with 18-36 months ADT? How many patients are expected to be in this group?
Some patients prefer orchiectomy over Hormonal therapy in our institute owing to financial and logistic constraints hence, we have included both modalities and stratified for the same.
Based on our previous data from the POP RT RCT ([Murthy V, Bhatia J, Kannan S, Gurav P, Krishnatry R, Chourasiya D, Prakash G, Bakshi G, Menon S, Mahantshetty U. PV-0629 Late toxicity and PROMs in pelvic or prostate RT in high risk prostate cancer: A randomized trial. Radiotherapy and Oncology. 2019 Apr 1;133: S335], we expect 20-25% patients who will undergo orchiectomy.

7. Exclusion criteria: why allow to include in the study patients with a life expectancy between 3 and 5 years? Please comment on that.
A. The life expectancy of less than 2 years was chosen as it acts as a surrogate for severe uncontrolled comorbid illnesses. In the Indian context, it is difficult to be precise about the life expectancy hence, the patients with the worst comorbidities are screened out.

8. Page 5: please add the stratification criteria
A. Stratification criteria added.

9. Page 7: treatment duration: please comment on OTT duration of 7 days with a treatment delivered every-other day (OTT expected minimum 9 days). Considering that OTT can impact tolerance of SBRT schedules (cfr King's series or the PATRIOT trial), it seems risky to extend the study protocol at the use of different OTT schedules.
A. The OTT is 7-10 days as one or 2 fractions are delivered on consecutive days (especially weekend). For Example: Monday, Wednesday, Friday, Saturday, Monday would be a typical example (or) Tuesday, Thursday, Saturday, Monday, Wednesday would be another. The 7-10 days range accounts for any unscheduled breaks/logistic issues/public holidays.

10. Page 8: are fiducials used for IGRT purposes? If invade, are the whole SV included in the high-dose volume.

A. Fiducials are not used for IGRT purposes similar to the PATRIOT Study by Dr. Andrew Loblaw. Seminal vesicles will be included in the high dose volume only if the said structure is involved in imaging. Contouring will be done as per the ESTRO ACROP Guidelines as referenced.

11. Please describe when EORTC or CTCAE grading scales are used (EORTC for acute and CTCAE for late side effects?)
A. CTCAE and RTOG/EORTC both will be used for grading Acute and Late toxicity assessment as there can be differences in the way toxicity is scored. RTOG is only for GU and Bowel whereas CTCAE encompasses various other toxicities. This has been added in the manuscript.

12. Pages 15 and 16: This section is a duplicate of the section already present on pages 13 and 14.
A. Duplicate section has been edited out.

13. Table 2. Doses constraints seems quite difficult to be achieved especially if the SV are included and nodes are boosted. Could you provide some data justifying the use of these dose constraints?
A. Dose constraints are based on institutional experiences and have been achievable and also the outcomes and toxicity published recently.

[Murthy V, Gupta M, Mulye G, Maulik S, Munshi M, Krishnatry R, et al. Early Results of Extreme Hypofractionation Using Stereotactic Body Radiation Therapy for High-risk, Very High-risk and Node-positive Prostate Cancer. Clin Oncol R Coll Radiol G B. 2018 Jul;30(7):442–7]
[Murthy V, Sinha S, Kannan S, Datta D, Das R, Bakshi G, Prakash G, Krishnatry R. Safety of Prostate Stereotactic Body Radiation Therapy after Transurethral Resection of Prostate (TURP): A Propensity Score Matched Pair Analysis. Practical Radiation Oncology. 2019 Apr 9]
[Murthy V, Bhatia J, Kannan S, Gurav P, Krishnatry R, Chourasiya D, Prakash G, Bakshi G, Menon S, Mahantshetty U. PV-0629 Late toxicity and PROMs in pelvic or prostate RT in high risk prostate cancer: A randomized trial. Radiotherapy and Oncology. 2019 Apr 1;133: S335].
14. Please comment on how the boost to the positive nodes is considered. This point is not clear and it can introduce large biases in the study.
A. Response assessment PSMA PETCT will be done for all patients with pelvic nodal disease to ascertain the response after approximately 6 months of ADT. Patients with persistent residual nodal disease defined as residual node ≥1cm in short axis and/or SUV max ≥ 3.0, nodal boost will be considered as a simultaneous integrated boost (SIB). In the standard arm, boost to residual gross nodal disease to a dose of 60-66Gy in 25 fractions will be considered. In the experimental arm, boost to gross residual nodal disease will be considered to a dose of 30-35Gy in 5 fractions. This explanation has been added in the manuscript.

15. Many references should be updated: ex ref 8 (published the last year on Lancet). Ref 7. Please add a reference for the PACE B study.
A. References updated and reference for PACE B study added.

16. Please add a table with the inclusion and exclusion criteria including the timeline of the study.
A. Table has been included. Timeline of this study is six years which is already mentioned in the Statistics section. The total study duration is six years with a non-fixed follow up period and a uniform accrual rate. This has been added in the manuscript.

VERSION 2 – REVIEW

REVIEWER	Glenn Bauman London Health Sciences Centre London, Ontario, Canada
REVIEW RETURNED	05-Dec-2019

GENERAL COMMENTS	The authors have modified their manuscript in accordance with the suggestions from the first review.

REVIEWER	Thomas ZILLI Geneva University Hospital, Geneva, Switzerland
REVIEW RETURNED	22-Dec-2019

GENERAL COMMENTS	The authors answered to the majority of reviewer's questions. Here some additional comments: 1. In the text they specified that "Nodal involvement by disease will be defined based on size, morphological characteristics and metabolic uptake by a specialist Uro Radiologist (PP) and Nuclear Medicine Specialist (VR, AA)". In the answer to reviewers, it is specified: " A suspicious node on PSMA PET CT is defined as having a dimension of ≥ 1cm in the short axis and SUVmax ≥ 3.0 based on the morphological and metabolic assessment by a Nuclear medicine specialist in Uro Radiology." Please clarify this point in the text as the majority of the PSMA + nodes have a size of < 1cm, that is the standard size to define a pathological node with standard imaging. 2. Duration of neoadjuvant ADT is not standardized (minimum of 8 weeks before the RT start). However, the authors state: "Response assessment PSMA PETCT will be done for all patients with pelvic nodal disease to ascertain the response after approximately 6 months of ADT. Patients with persistent residual nodal disease defined as residual node ≥1cm in short axis and/or SUV max ≥ 3.0, nodal boost will be considered as a simultaneous integrated boost (SIB)." Considering the above comments on the N+ assessment and a PSMA assessment done at 6 mo after ADT start, the authors should better clarify this point as it remains unclear. 3. On page 18, please cite the new ESTRO-ACROP guidelines for prostate IGRT (Ghadjar P et al. Radiother Oncol. 2019 Dec;141:5-13. PMID:31668515)

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 2: Thomas Zilli

1. Nodal involvement by disease will be defined as SUVmax ≥ 3.0 irrespective of the size but based on morphological characteristics like shape, heterogeneity and perinodal stranding as determined by expert in Uro Radiology (PP) and Nuclear Imaging (VR, AA).

2. The duration of neoadjuvant ADT ranges from about 8-12 weeks for node negative patients and 6 months for node positive patients to assess nodal response.

3. The new ESTRO-ACROP prostate IGRT guideline has been cited on page 18.

These changes have been incorporated into the manuscript.

VERSION 3 - REVIEW

REVIEWER	Thomas ZILLI Geneva University Hospital, Geneva, Switzerland
REVIEW RETURNED	22-Jan-2020

GENERAL COMMENTS	The authors answered to all questions/suggestions of teh last review